PATENT SPECIFICATION

NO DRAWINGS

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872,447

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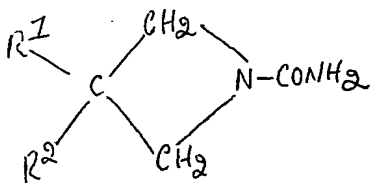
COMPLETE SPECIFICATION

1-Carbamyl-3-Substituted Azetidines

We, LEPETIT S.P.A., an Italian Body Corporate, of 10, Via Roberto Lepetit, Milan, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

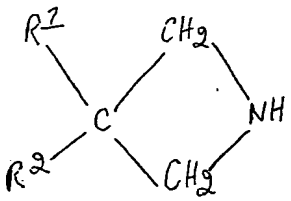
This invention is concerned with new pharmacologically active compounds. More particularly, the invention is concerned with new carbamylazetidines of the formula:—



wherein R^1 represents hydrogen, a lower alkyl, comprising 1 to 8 carbon atoms, cycloalkyl, phenyl or phenylalkyl radical and R^2 represents a lower alkyl, comprising 1 to 8 carbon atoms, cycloalkyl, phenyl or phenylalkyl radical.

The compounds of the invention are active as sedatives, hypnotics and antispasmodic agents. This last effect is particularly high with 1-carbamyl-3-propylazetidine, 1-carbamyl - 3 - phenyl - 3 - isopropylazetidine and 1 - carbamyl - 3 - phenyl - 3 - methylazetidine, which already in doses lower than 20 mg./kg. prevent convulsive seizures induced by pentamethylenetetrazole. The average lethal dosage LD_{50} is very high, in all cases exceeding 300—400 mg./kg. on intraperitoneal administration to rats.

The process for the preparation of the new compounds consists in reacting for some minutes the hydrochloride of a 3-substituted azetidine of the formula:—



wherein R^1 and R^2 have the above significance, with an equimolecular amount of an alkali metal cyanate in water at 50—100° C. After cooling, generally an oil separates, which after some time crystallises. The product is collected and if desired recrystallised from a suitable solvent. Yields are generally very satisfactory.

The starting compounds, i.e., the 3-substituted azetidines, are prepared according to the procedure described and claimed in our copending patent application No. 41523/58 (Serial No. 872,446).

The following examples are illustrative of the invention.

EXAMPLE 1.

A suspension of 32 g. of 3-phenyl-3-ethylazetidine in 100 ml. water is treated firstly with 100 ml. of *2N* hydrochloric acid, and then with 13 g. of sodium cyanate. The mixture is then heated for 15 minutes to 50—60° C. An oil gradually separates, which after cooling crystallises. The product is collected and recrystallised from 5 per cent ethanol. Yield 36 g. (88%) of 1-carbamyl-3-phenyl-3-ethylazetidine; m.p. 154—156° C.

EXAMPLE 2.

A solution of 18.35 g. of 3-phenyl-3-methylazetidine hydrochloride in 100 ml. of water is heated to 50—60° C. for 15 minutes with 6.5 g. of sodium cyanate. The product which separates as an oil, solidifies on cooling and is collected. Yield 17 g. (90%) of 1-carbamyl-3-phenyl-3-methylazetidine; m.p. 176° C. (from dilute ethanol).

EXAMPLE 3.

A solution of 17 g. of 3-phenylazetidine hydrochloride in 100 ml. water is heated for 10 minutes to 60—65° C. with 6.5 g. of sodium cyanate. After cooling the product is collected and recrystallised from ethanol. Yield 14 g. (80%) of 1-carbamyl-3-phenylazetidine; m.p. 231—233° C.

EXAMPLE 4.

A solution of 15 g. of 3,3-diethylazetidine in 100 ml. of water is heated for 20 minutes to 55—60° C. with 6.5 g. of sodium cyanate. After cooling the formed precipitate is collected and recrystallised from dilute ethanol. Yield 12 g. (77%) of 1-carbamyl-3,3-diethylazetidine; m.p. 179—180°.

EXAMPLE 5.

A suspension of 21.2 g. of 3-phenyl-3-propylazetidine in 100 ml. of water is heated with 5.6 g. of sodium cyanate for 15 minutes to 50—60° C. After cooling the formed product is collected and recrystallised from dilute ethanol. Yield 19 g. (87%) of 1-carbamyl-3-phenyl-3-propylazetidine; m.p. 165—166° C.

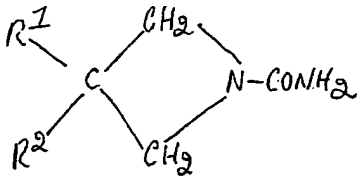
EXAMPLES 6 TO 10.

According to the process of the preceding examples the following 1 - carbamyl-azetidines were produced from the corresponding azetidines. Yields (y.) and melting points (m.p.) are given:

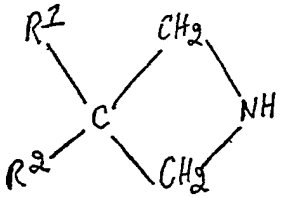
3-phenyl-3-benzyl	y. 81%	m.p. 159—161° C.
3,3-dibutyl	y. 90%	m.p. 114—115° C.
3-phenyl-3-butyl	y. 75%	m.p. 129—131° C.
3-phenyl-3-isopropyl	y. 86%	m.p. 158—160° C.
3-phenyl-3-cyclohexyl	y. 62%	m.p. 172—174° C.

WHAT WE CLAIM IS:—

1. A process for preparing a compound of the formula:—



wherein R^1 represents hydrogen, a lower alkyl, comprising 1 to 8 carbon atoms, cycloalkyl, phenyl or phenylalkyl radical and R^2 represents a lower alkyl, comprising 1 to 8 carbon atoms, cycloalkyl, phenyl or phenylalkyl radical, which comprises heating the hydrochloride of an azetidine of the formula:—



wherein R^1 and R^2 have the above significance, with an equimolecular amount of an alkali metal cyanate in water at a temperature between 50 and 100° C.

2. A process as in claim 1, wherein the alkali metal cyanate is sodium cyanate.

3. A process as in claim 1, wherein 3-phenyl-3-ethylazetidine is employed as the starting material.

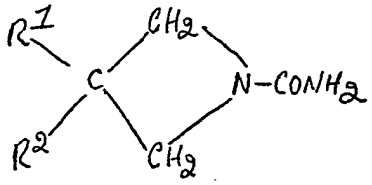
4. A process as in claim 1, wherein 3-phenyl-3-methylazetidine is employed as the starting material.

5. A process as in claim 1, wherein 3-phenylazetidine is employed as the starting material.

6. A process as in claim 1, wherein 3-propylazetidine is employed as the starting material.

7. A process as in claim 1, wherein 3-phenyl-3-isopropylazetidine is employed as the starting material.

8. A compound of the formula:—



wherein R^1 represents hydrogen, a lower alkyl, comprising 1 to 8 carbon atoms, cycloalkyl, phenyl or phenylalkyl radical and R^2 represents a lower alkyl, comprising 1 to 8 carbon atoms, cycloalkyl, phenyl or phenylalkyl radical.

9. 1 - Carbamyl - 3 - phenyl - 3 - ethylazetidine.

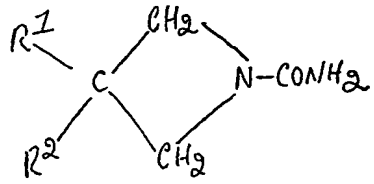
10. 1 - Carbamyl - 3 - phenyl - 3 - methylazetidine.

11. 1-Carbamyl-3-phenylazetidine.

12. 1-Carbamyl-3-propylazetidine.

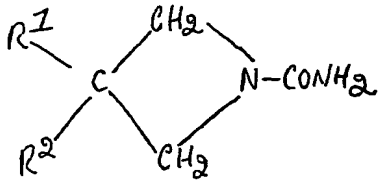
13. 1 - Carbamyl - 3 - phenyl - 3 - isopropylazetidine.

14. A process for the preparation of a compound of the formula:—



wherein R^1 represents hydrogen, a lower alkyl, comprising 1 to 8 carbon atoms, cycloalkyl, phenyl or phenylalkyl radical and R^2 represents a lower alkyl, comprising 1 to 8 carbon atoms, cycloalkyl, phenyl or phenylalkyl radical, substantially as herein described with reference to any of the examples.

15. A compound of the formula:



wherein R^1 represents hydrogen, a lower alkyl, comprising 1 to 8 carbon atoms, cycloalkyl, phenyl or phenylalkyl radical and R^2 represents a lower alkyl, comprising 1 to 8 carbon atoms, cycloalkyl, phenyl or phenylalkyl radical when prepared by a process as claimed in any of claims 1 to 7 or 14.

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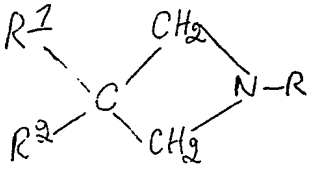
PROVISIONAL SPECIFICATION

1-Carbamyl-3-Substituted Azetidines

We, LEPETIT S.P.A., an Italian Body Corporate, of 10, Via Roberto Lepetit, Milan, Italy, do hereby declare this invention to be described in the following statement:—

This invention is concerned with new pharmacologically active compounds. More particularly, the invention is concerned with new 3,3-disubstituted azetidines of the formula

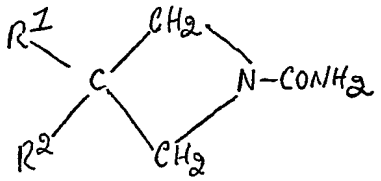


wherein R represents carbamyl, R^1 represents a lower alkyl radical and R^2 represents phenyl or ethyl radicals.

The compounds of the invention have been found to possess useful pharmacological properties. Some of the compounds are active as sympathomimetics. Others are sedatives. Still others are central nervous system stimulants.

The methods for preparing compounds of the invention vary according to the significance of R. The best procedure for obtaining the derivatives in which R is hydrogen is to hydrogenate the corresponding 2-azetidinones with lithium aluminium hydride in a solvent. The starting 2-azetidinones are described and claimed in our British Specification No. 829,663.

The *N*-unsubstituted azetidines thus produced are then used for preparing other compounds of the invention. The azetidines, when reacted with sodium cyanate, yield the N-carbamyl compounds:



Example 1: 1 - carbamyl - 3 - ethyl - 3-phenylazetidine. A mixture of 3.2 g. of 3-ethyl-3-phenylazetidine, 20 ml. of *N* hydrochloric acid and 1.3 g. of sodium cyanate is warmed at 50/60° for 15 minutes on a water bath. After cooling the formed precipitate is collected. Yield 3.6 g., m.p. 154—156°.

Example 2: 1 - carbamyl - 3 - phenyl - 3-methylazetidine. This compound is prepared as described in the preceding example starting from 3 g. of 3-phenyl-3-methylazetidine. Yield 2.5 g., m.p. 176°.

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